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Infliximab in the Treatment of Crohn's Disease: A User's Guide for Clinicians

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ABSTRACT

Induction therapy with infliximab is indicated for treatment of signs and symptoms, and induction and maintenance of remission in patients with moderate to severely active inflammatory Crohn's disease with an inadequate response to conventional therapy, and for reduction in the number of draining fistulas in patients with fistulizing Crohn's disease. Emerging indications for infliximab therapy in patients with Crohn's disease include maintenance of fistula improvement (reduction in the number of draining perianal or enterocutaneous fistulas) and complete fistula response (no draining fistulas) in patients with fistulizing Crohn's disease, steroid sparing in steroid-treated patients, early use in hospitalized patients who have not failed conventional medical therapy where there is either a severe clinical presentation or a rapid onset of action is desired, and in a variety of unusual and extra-intestinal manifestations of Crohn's disease. An infliximab dose of 5 mg/kg is recommended initally, but some patients who require maintenance dosing may benefit from increasing the infliximab dose over a range of 5–10 mg/kg. An induction regimen of 3 doses at 0, 2, and 6 weeks is the preferred dosing strategy for inducing remission. The optimal dosing interval for patients who require retreatment appears to be every 8 weeks for most patients. Concomitant immunosuppressive therapy with azathioprine, 6-mercaptopurine, or methotrexate may result in improved outcomes due to a reduction in the frequency of human anti-chimeric antibody formation, acute infusion reactions, and a reduced risk of delayed hypersensitivity-like reactions and formation of antinuclear antibodies. Pretreatment with diphenhydramine (and in selected cases of acetaminophen and, rarely, corticosteroids) is recommended in patients with a history of infusion reactions and patients at risk for delayed hypersensitivity-like reactions. Patients with evidence of active infection should not receive infliximab until the infection is adequately treated, and all patients should be screened for tuberculosis prior to initiating infliximab therapy (Am J Gastroenterol 2002;97:2962–2972. © 2002 by Am. Coll. of Gastroenterology)

INTRODUCTION

The chimeric monoclonal antibody to tumor necrosis factor α, infliximab, is an effective treatment for Crohn's disease. As the first biological therapy approved for this disease, clinicians must be familiar with the indications for induction and maintenance therapy, and understand appropriate dosing, *i.v.* administration, and issues related to concomitant medical and surgical therapy. Similarly, clinicians must be knowledgeable regarding the presentation, management, and prevention of adverse events including infusion reactions, delayed hypersensitivity-like reactions, and the potential for rare events such as reactivation of latent tuberculosis and the development of drug-induced lupus. This article reviews the definite and potential treatment indications for infliximab in patients with Crohn's disease, and provides a literature-based "user's guide for clinicians" to address the issues outlined above.

INDICATIONS FOR TREATMENT

Induction Therapy With Infliximab

Clinicians should seek to achieve one or more of the following treatment goals when initiating induction therapy with infliximab in patients with Crohn's disease: 1) induction of clinical improvement or clinical remission; 2) fistula improvement (reduction in the number of draining perianal or enterocutaneous fistulas) or complete fistula response (no draining fistulas); 3) steroid-sparing in steroid-treated patients; or 4) avoidance of steroid therapy entirely, using infliximab as a rapidly acting induction therapy followed by maintenance treatment with azathioprine, 6-mercaptopurine, or methotrexate. Improvement of nutritional status in patients undernourished because of disease activity may also be a reasonable goal. The "approved" indications for induction therapy with infliximab (according to regulatory approval by the United States Food and Drug Administration

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Table 1. Definite and Potential Treatment Indications for Infliximab in Patients With Inflammatory Bowel Disease

Definite indications for induction therapy with infliximab
1. Moderate-to-severe inflammatory Crohn's disease with an inadequate response to conventional therapy (defined by severity of symptoms and/or lack of response to standard therapy such as corticosteroids, azathioprine, 6-mercaptopurine, and methotrexate)
2. Fistulizing Crohn's disease with draining enterocutaneous or perianal fistulas
Potential indications for induction therapy with infliximab
1. Hospitalized patients with inflammatory or fistulizing Crohn's disease who have not failed all conventional therapies where there is either a severe clinical presentation or a rapid onset of action is desired
2. Pediatric Crohn's disease
3. Steroid-treated Crohn's disease (a form of maintenance therapy)
4. Other manifestations of Crohn's disease (Crohn's disease of the ileoanal pouch, ankylosing spondylitis and sacroiliitis, pyoderma gangrenosum, Crohn's disease-associated arthritis, metastatic and perineal wound Crohn's disease, orofacial Crohn's disease, esophageal Crohn's disease)
5. Moderate-to-severe ulcerative colitis unresponsive to conventional therapy
6. Severe, steroid-refractory ulcerative colitis
Definite indications for maintenance therapy with infliximab
1. Inflammatory or fistulizing Crohn's disease that responded to initial induction therapy with infliximab and failed maintenance therapy with one or more immunosuppressive agents
2. Steroid-treated Crohn's disease that failed an attempt at steroid sparing with one or more immunosuppressive agents

[FDA] in the United States and/or the European Agency for the Evaluation of Medicinal Products in Europe) are: 1) reduction in signs and symptoms and induction of clinical remission in patients with "moderately to severely" active inflammatory Crohn's disease where there is an inadequate response to conventional therapy (in Europe, this is defined as failure to respond to both steroids and immunosuppressive agents); and 2) reduction in the number of draining enterocutaneous fistulas in patients with fistulizing Crohn's disease (Table 1). The designation "moderately to severely" active can be based on the severity of clinical symptoms and/or inadequate response to standard therapies such as aminosalicylates, antibiotics, corticosteroids, azathioprine, 6-mercaptopurine, or methotrexate (1). These approvals for marketing are based on a study by Targan *et al.* demonstrating clinical remission achieved by 48% of patients with active inflammatory Crohn's disease treated with infliximab at a dose of 5 mg/kg at 4 wk compared with only 4% of placebo-treated patients (2), a study by Hanauer *et al.* demonstrating clinical response achieved by 57% of patients with active inflammatory Crohn's disease treated with infliximab 5 mg/kg at 2 wk (3), and a study by Present *et al.* demonstrating a $\geq$50% reduction in the number of drainage of enterocutaneous or perianal fistulas for at least 4 wk in 55% of patients compared with only 13% of placebo-treated patients (4).

A number of potential "inductive" indications for infliximab therapy of Crohn's disease are based on additional uncontrolled case reports, case series, and placebo-controlled trials (Table 1). There is anecdotal experience that infliximab may be useful in hospitalized patients with severe inflammatory or fistulizing Crohn's disease requiring a rapidly acting agent, even if these patients have not failed standard therapies. The goal for infliximab in this setting is rapid induction of remission followed by maintenance treatment with azathioprine, 6-mercaptopurine, or methotrexate. There is also evolving experience in pediatric patients suggesting that infliximab has similar efficacy and dose response as in adult patients (5–7). Thus, infliximab is now used by pediatric gastroenterologists in selected cases, for indications similar to those used in adult patients. Infliximab has been useful as a steroid-sparing agent in patients with steroid-treated Crohn's disease (3, 8, 9) when repeated doses are administered over a prolonged period, and thus is a form of retreatment, or maintenance, that will be discussed in detail below. Other, less frequent, manifestations of Crohn's disease reported to benefit from induction therapy with infliximab include Crohn's disease of the ileoanal pouch (10), ankylosing spondylitis and sacroiliitis (11–14), pyoderma gangrenosum (15, 16), Crohn's disease-associated arthritis (17), metastatic and perineal wound Crohn's disease (18, 19), orofacial Crohn's disease (20), and esophageal Crohn's disease (21, 22). Treatment with infliximab may also result in improved nutritional status in patients undernourished because of disease activity, an effect that is particularly important in pediatric patients. There are several small uncontrolled studies of infliximab therapy for patients with moderate-to-severe ulcerative colitis unresponsive to medical therapy (23, 24) as well as a small placebo-controlled trial in 11 hospitalized patients with severe steroid refractory ulcerative colitis (25), which suggest that infliximab may be beneficial for the treatment of ulcerative colitis. However, another placebo-controlled trial of infliximab in 42 patients with steroid-refractory ulcerative colitis failed to demonstrate a benefit (26). Phase III placebo-controlled trials are ongoing to clarify these discrepant results. In the interim, the efficacy of infliximab for the treatment of ulcerative colitis is indeterminate.

Maintenance Therapy With Infliximab

Clinicians should seek to achieve one or more of the following treatment goals when initiating maintenance therapy with infliximab in patients with Crohn's disease: 1) maintenance of clinical improvement or clinical remission; 2) maintenance of fistula improvement (reduction in the number of draining perianal or enterocutaneous fistulas) or com-

plete fistula response (no draining fistulas); 3) steroid sparing; 4) discontinuation of minimally effective drugs such as sulfasalazine, mesalamine, and antibiotics; and 5) avoidance of major surgical resections (particularly where there is extensive small bowel involvement or where proctectomy would be required). Maintenance of improved nutritional status in patients previously undernourished because of disease activity is also a reasonable goal.

The "approved" indication for maintenance therapy with infliximab (according to regulatory approval by the FDA in the United States; review by the European Agency for the Evaluation of Medicinal Products in Europe is pending) is maintenance of clinical improvement and clinical remission in patients who previously had moderately to severely active inflammatory Crohn's disease with an inadequate response to conventional therapy who responded to initial induction therapy with infliximab. Indications for maintenance therapy with infliximab (based on controlled trials that currently precede regulatory approval by the FDA in the United States and the European Agency for the Evaluation of Medicinal Products in Europe) include: 1) maintenance of fistula improvement (reduction in the number of draining perianal or enterocutaneous fistulas) and complete fistula response (no draining fistulas) in patients with fistulizing Crohn's disease who responded to initial induction therapy with infliximab; and 2) steroid sparing in patients with steroid-treated Crohn's disease who have failed an attempt at steroid sparing with one or more immunosuppressive agents (Table 1). The recommendations for maintenance therapy with infliximab are based on three placebo-controlled trials. Rutgeerts *et al*. demonstrated beneficial effects with infliximab maintenance dosing 10 mg/kg every 8 wk for four doses (27). Hanauer *et al*. demonstrated significantly greater rates for maintenance of both clinical remission and clinical response over 54 wk in patients retreated with infliximab either 5 mg/kg or 10 mg/kg every 8 wk compared with retreatment with placebo (3). In this study, the median time to loss of response was 19 wk for patients who received a single dose of infliximab and were then retreated with placebo, compared with 38 wk for patients who received infliximab 5 mg/kg every 8 wk and >54 wk for patients who received infliximab 10 mg/kg every 8 wk. This study also demonstrated a statistically significant benefit for maintenance of clinical remission and complete steroid withdrawal in the subset of patients who were receiving steroids at baseline (3). By wk 30, the median steroid dose for patients who received only a single dose of infliximab was 10 mg per day compared with 0 mg per day for patients receiving infliximab either 5 or 10 mg/kg every 8 wk. Data from this controlled trial confirm earlier uncontrolled observations from two large case series that infliximab is steroid sparing (8, 9). It should be emphasized that attempts to discontinue long-term steroid therapy with prednisone at any dose, or budesonide at doses >6 mg, are now standard of care given the proven efficiency of azathioprine, 6-mercaptopurine, methotrexate, and infliximab for steroid sparing (3, 28–31). In the third controlled trial, Sands *et al*. demonstrated significantly greater rates for the maintenance of both fistula improvement (reduction in the number of draining fistulas) and fistula remission (no draining fistulas) over 54 wk in patients retreated with infliximab 5 mg/kg every 8 wk compared with retreatment with placebo (32). In this study, the median time to loss of response was 14 wk for patients who received three induction doses of infliximab at weeks 0, 2, and 6 and were then retreated with placebo, compared with >40 wk for patients who received infliximab 5 mg/kg every 8 wk. In clinical practice, given that most patients treated with infliximab have had an inadequate response to conventional therapy (33), and that the relapse rates after discontinuation of infliximab in patients with either inflammatory or fistulizing Crohn's disease who required infliximab for treatment for active symptoms or draining fistulas are quite high (3, 32), a majority of patients who initiate treatment with infliximab will require long-term maintenance therapy.

DOSING AND ADMINISTRATION OF INFLIXIMAB

Dose

In the initial dose finding studies for induction of remission or reduction in the number of draining fistulas in patients with active Crohn's disease, an infliximab dose of 5 mg/kg gave greater response and remission rates than either 1 mg/kg on the low side, or 10 mg/kg and 20 mg/kg on the higher side (2, 4, 34). However, in a recent large maintenance trial in patients with Crohn's disease, infliximab 10 mg/kg was slightly superior to 5 mg/kg, with both infliximab doses showing significantly better maintenance of remission rates than placebo (3). Based on these data, it seems that the optimal infliximab dose for induction of remission in patients with active Crohn's disease is 5 mg/kg. For maintenance dosing, clinicians should start with a dose of 5 mg/kg. In individual patients in whom the duration of benefit seems to be fewer than 8 wk, or in patients where the magnitude of benefit seems to be attenuated or lost, the dose may be customized over a range of 5–10 mg/kg, and/or the dosing interval may be shortened (see below) to optimize the response to treatment (33, 35). One strategy for increasing the dose is to round up to the nearest 100-mg increment (100-mg vials), increasing the dose further as needed in 100-mg increments up to a maximal dose of 10 mg/kg. A suggested algorithm for the routine infusion of infliximab is shown in Figure 1. Equipment required to administer infliximab includes an infusion pump and an infusion set with an in-line, sterile, nonpyrogenic, low protein-binding filter (pore size of 1.2 μm or less) (33). Equipment required to manage infusion reactions will be discussed below.

Dosing Regimen

There has been some confusion regarding induction dosing between the four pivotal trials of infliximab for active inflammatory and fistulizing Crohn's disease. In the initial induction of remission study for patients with active inflam-

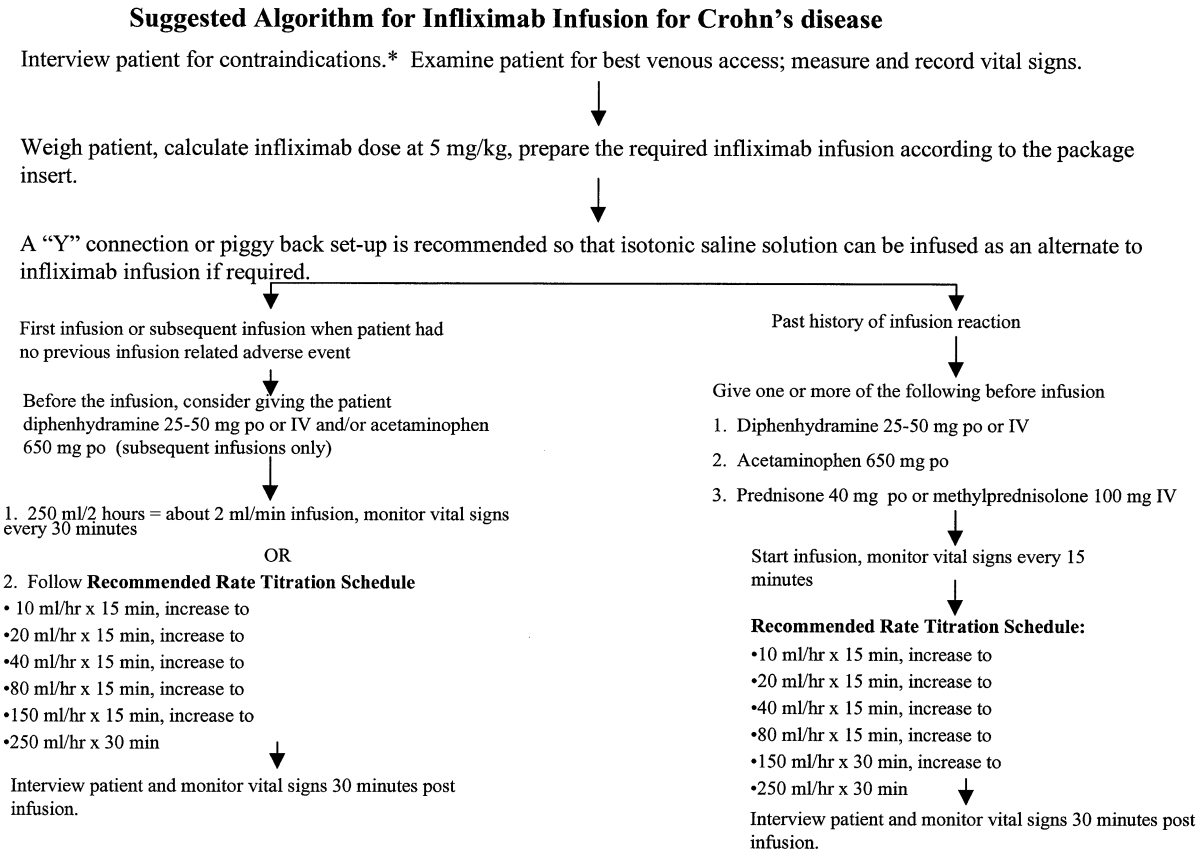
Suggested Algorithm for Infliximab Infusion for Crohn's disease
Interview patient for contraindications.* Examine patient for best venous access; measure and record vital signs.
Weigh patient, calculate infliximab dose at 5 mg/kg, prepare the required infliximab infusion according to the package insert.
A "Y" connection or piggy back set-up is recommended so that isotonic saline solution can be infused as an alternate to infliximab infusion if required.
First infusion or subsequent infusion when patient had no previous infusion related adverse event
Before the infusion, consider giving the patient diphenhydramine 25-50 mg po or IV and/or acetaminophen 650 mg po (subsequent infusions only)
1. 250 ml/2 hours = about 2 ml/min infusion, monitor vital signs every 30 minutes
OR
2. Follow Recommended Rate Titration Schedule
• 10 ml/hr x 15 min, increase to
•20 ml/hr x 15 min, increase to
•40 ml/hr x 15 min, increase to
•80 ml/hr x 15 min, increase to
•150 ml/hr x 15 min, increase to
•250 ml/hr x 30 min
Interview patient and monitor vital signs 30 minutes post infusion.
Past history of infusion reaction
Give one or more of the following before infusion
1. Diphenhydramine 25-50 mg po or IV
2. Acetaminophen 650 mg po
3. Prednisone 40 mg po or methylprednisolone 100 mg IV
Start infusion, monitor vital signs every 15 minutes
Recommended Rate Titration Schedule:
•10 ml/hr x 15 min, increase to
•20 ml/hr x 15 min, increase to
•40 ml/hr x 15 min, increase to
•80 ml/hr x 15 min, increase to
•150 ml/hr x 30 min, increase to
•250 ml/hr x 30 min
Interview patient and monitor vital signs 30 minutes post infusion.
*Infliximab should not be administered to patients with known hypersensitivity to any murine proteins or other component of the product.

Figure 1. Suggested algorithm for infliximab infusion in patients with Crohn's disease.

matory Crohn's disease, a single infliximab infusion was administered (2). In contrast, in patients with rheumatoid arthritis, and in patients with fistulizing Crohn's disease, a three-dose induction sequence has been used with doses administered at 0, 2, and 6 wk, with subsequent doses every 4–8 wk (4, 32, 36, 37). Another large trial in patients with active inflammatory Crohn's disease compared one-dose *versus* three-dose induction strategies, and found that the clinical response rates at 10 wk were 65% for patients who received three-dose induction compared with 52% for patients who received one-dose induction therapy (3, 38). Whether the improved clinical response rate at 10 wk in patients treated with three induction doses represents a true advantage for the three-dose induction group or simply reflects a gradual loss of response by wk 10 in patients who received a single infusion is unclear. Some investigators have proposed the hypothesis that patients who receive three-dose induction therapy may develop an immunological "tolerance" to infliximab, whereas patients who receive a single infliximab infusion may become sensitized or "immunized." The rationale and expanding experience is that patients who receive a three-dose induction sequence may be less likely to form human antichimeric antibodies (HACA) (see below), or to develop infusion reactions or delayed hypersensitivity reactions (see below) (36, 39, 40). This hypothesis is to some degree borne out by the results of a clinical trial of maintenance dosing with infliximab every 8 wk for 1 yr in patients with rheumatoid arthritis (following a three-dose induction at 0, 2, and 6 wk) where severe infusion reactions and delayed hypersensitivity reactions have not been observed (41). For all of these reasons, a three-dose induction regimen at 0, 2, and 6 wk is the preferred induction strategy, and in the United States, the FDA-approved recommended dose is 5 mg/kg given as an induction regimen at 0, 2, and 6 wk (33). Nevertheless, it should be acknowledged that this strategy (three-dose induction at weeks 0, 2, and 6) *versus* a seemingly rational alternative of one-dose induction with a second dose at wk 2 only in those not responding at wk 2 has not been formally tested as the primary endpoint in a randomized controlled trial.

Dosing Interval

The half-life of infliximab after 5 or 10 mg/kg doses is 8–10 days (33). After a single *i.v.* infusion, most patients receiving a 5- mg/kg dose have therapeutic infliximab concentrations at 8 wk and undetectable concentrations at 12 wk, whereas in patients receiving 10 mg/kg, therapeutic inflix-

imab concentrations are usually present through 12 wk (33, 42). Consistent with these pharmacokinetic characteristics, the duration of benefit after a single infusion of infliximab seems to be 8–12 wk for many patients (27). Both clinical experience and clinical trials have suggested that many patients will relapse after 8 wk, and will subsequently require retreatment or maintenance therapy on an approximate 8-wk dosing interval (more or less for individual patients) to prevent or treat recurrence of symptoms (3, 8, 9, 27, 32). A large study in patients with rheumatoid arthritis evaluating infliximab doses of 3 mg/kg and 10 mg/kg every 4 wk and every 8 wk suggested that there was no advantage to every 4-wk dosing over every 8-wk dosing (37). However, there were, at least, numerical advantages, if not statistical, for patients receiving 10 mg/kg *versus* 3 mg/kg every 8 wk. These data again suggest that the pharmacokinetics of infliximab correlate to the duration of response in individual patients. Thus, for most patients, an every 8-wk dosing interval will be ideal. In individual patients in whom the duration of benefit seems to be fewer than 8 wk, or in patients where the magnitude of benefit seems to be attenuated or lost, a customized dosing regimen can be developed by shortening the dosing interval to every 6 wk and in some cases every 4 wk and/or increasing the dose up to 10 mg/kg (see above) to optimize the individual response to treatment (33, 35).

Concomitant Medical Therapy and Surgery

In patients with rheumatoid arthritis, combination therapy with infliximab and methotrexate yields superior clinical outcomes and results in a lower incidence of HACA compared with monotherapy with infliximab (36). Thus, in this disease setting, infliximab and methotrexate are routinely coadministered. In patients with Crohn's disease, the coadministration of concomitant immunosuppressive therapy has not been as well studied. In the acute studies in active or fistulizing Crohn's disease, there was no short-term advantage to concurrent administration of an immunomodulator (2, 4). However, in the "retreatment" study by Rutgeerts *et al.*, the addition of an immunomodulator was associated with a prolonged benefit from infliximab (27). Furthermore, in a recent controlled trial, the remission rates at 30 wk were greater in patients receiving infliximab 5 mg/kg or 10 mg/kg in combination with azathioprine, 6-mercaptopurine, or methotrexate, suggesting either synergy or decreased immunogenicity (see below) with immunosuppressive drugs (3, 43). For these reasons, but primarily to decrease immunogenicity and formation of antinuclear antibodies (ANA) and antidouble-stranded antibodies (see below), the authors routinely coadminister an immunosuppressive agent (azathioprine, 6-mercaptopurine, or methotrexate) with infliximab. In patients who have previously failed all of these agents but were not intolerant, one of the immunosuppressive medications is typically restarted, again primarily because of the decreased immunogenicity and formation of ANA and antidouble-stranded antibodies in patients concomitantly treated with an immunosuppressive agent. The duration of "pretreatment" required with purine antimetabolite or methotrexate has not been evaluated, and there may be different prerequisites according to the class of immunomodulators. The exception to this strategy would be for patients who are intolerant to all of the immunosuppressive medications. Although the authors routinely coadminister an immunosuppressive agent with infliximab for the reasons outlined above, it should be acknowledged that the subset of patients with Crohn's disease treated with infliximab in clinical trials who did not receive concomitant immunosuppressive or corticosteroid therapy (and thus essentially received monotherapy with infliximab) did have a clinical response (2–4, 27).

The safety and benefit of perioperative administration of infliximab (within 8 wk before operation or 6 wk after operation) in patients with Crohn's disease undergoing laparotomy has not been well studied, but clinical experience has yet to identify increased rates of perioperative infection or problems with wound healing. However, the administration of infliximab should be delayed in patients with known abdominal or pelvic abscess or urosepsis complicating an enterovesical fistula and in patients with other active infections, until the infection has been adequately treated. For patients with perianal Crohn's disease, perioperative administration of infliximab to patients who require perianal surgical procedures (examination under anesthesia, incision and drainage of perianal abscess, placement of mushroom catheter, fistulotomy, placement of noncutting setons, rectal advancement flap) has been practiced by one of our centers (the Mayo Clinic), and again clinical experience suggests that there are not increased rates of perioperative infection or problems with wound healing. A combined medical and surgical therapeutic strategy in which patients undergo a diagnostic evaluation with examination under anesthesia (and possibly anorectal ultrasound or pelvic magnetic resonance imaging), surgical therapy (incision and drainage of perianal abscesses and placement of noncutting setons in all fistula tracts), and medical therapy (azathioprine or 6-mercaptopurine combined with infliximab and possibly an antibiotic such as metronidazole or ciprofloxacin) may be the optimal treatment approach (44, 45). The rationale for the temporary placement of noncutting setons is to prevent the cutaneous orifice of the fistula from closing prematurely, before the internal portion of the fistula tract has closed, leading to perianal abscess formation as a complication of infliximab therapy (in one study, this event occurred in 11% of patients treated with infliximab) (4). In patients who have had noncutting setons placed, the setons will ultimately have to be removed for the fistulas to close after cessation of draining. Based on clinical experience, the authors recommend that perianal setons be removed approximately 2–6 wk after successful control (cessation) of fistula drainage. In most cases, however, continued infliximab therapy will be necessary to control or prevent recurrent fistula discharge.

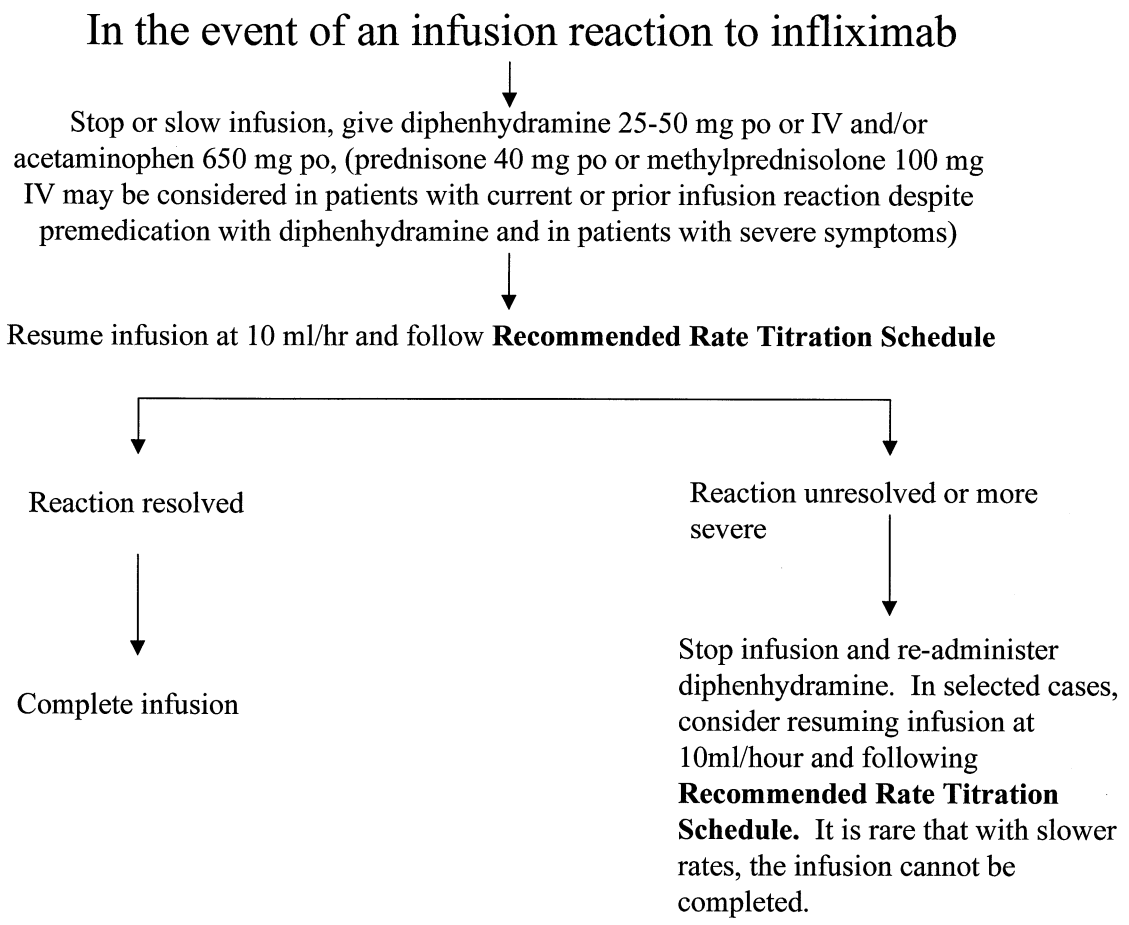
In the event of an infusion reaction to infliximab
Stop or slow infusion, give diphenhydramine 25-50 mg po or IV and/or acetaminophen 650 mg po, (prednisone 40 mg po or methylprednisolone 100 mg IV may be considered in patients with current or prior infusion reaction despite premedication with diphenhydramine and in patients with severe symptoms)
Resume infusion at 10 ml/hr and follow **Recommended Rate Titration Schedule**
Reaction resolved
Complete infusion
Reaction unresolved or more severe
Stop infusion and re-administer diphenhydramine. In selected cases, consider resuming infusion at 10ml/hour and following **Recommended Rate Titration Schedule.** It is rare that with slower rates, the infusion cannot be completed.

Figure 2. Suggested algorithm for managing infusion-related reactions to infliximab in patients with Crohn's disease.

PREVENTION AND MANAGEMENT OF ADVERSE EVENTS

Infusion Reactions and Delayed Hypersensitivity-Like Reactions

There are a number of treatment strategies that can be employed to reduce the frequency of infusion reactions and possibly delayed hypersensitivity-like reactions. These strategies include using the three-dose (0, 2, and 6 wk) induction regimen discussed above (with the goal of inducing immunological tolerance to infliximab), considering every 8 wk maintenance dosing for at least several doses after the induction sequence (again with the goal of inducing immunological tolerance to infliximab), routinely coadministering an immunosuppressive drug such as azathioprine, 6-mercaptopurine, or methotrexate (even if the patient has previously failed all of these medications) with the goals of possible synergistic response and blunting the patient's immune response to infliximab, and considering premedication with diphenhydramine (and in some patients acetaminophen and/or steroids), especially in patients who have a history of infusion reactions and/or in whom there has been a long hiatus (6 months or more) from a previous infliximab infusion.

Acute infusion reactions to infliximab, which are anaphylactoid (non-IgE mediated) (46) and similar to those observed with administration of other proteins including *i.v.* immune globulins (47), include symptoms of dyspnea, chest tightness, urticaria, and headache (33). The incidence of acute infusion reactions is approximately 22% in infliximab-treated patients compared with 9% in placebo-treated patients (33). Acute infusion reactions are more common in patients who are HACA positive (see below) (33). Acute infusion reactions are relatively less common in patients receiving concomitant immunosuppressive therapy (possibly related to a decreased frequency of HACA response) (33). Suggested algorithms for the routine infusion of infliximab and for managing acute infusion reactions are shown in Figures 1 and 2. In general, the treatment of an acute infusion reaction consists of temporarily stopping the infusion, treatment with diphenhydramine 25–50 mg *p.o.* or *i.v.* (± acetaminophen 650 mg *p.o.*), waiting for the symptoms to resolve, and then restarting the infusion at a slower rate. It should be emphasized that normal infusion rates of 250 ml over 2 h may be too rapid for some patients, and that slowing the infusion rate seems to be an important part of managing infusion reactions. One of the authors (W.J.S.) often administers prednisone 40 mg *p.o.* or methylpred-

nisolone 100 mg *i.v.* in this setting in addition to diphenhydramine. Using this treatment strategy, most patients who experience an infusion reaction can complete the infusion. In patients who have a history of infusion reactions, pretreatment with 25–50 mg of *p.o.* or *i.v.* diphenhydramine (again ± 650 mg of acetaminophen and/or 40 mg of *p.o.* prednisone or 100 mg of *i.v.* methylprednisolone), and initiating the subsequent infusions at a slower rate, will allow most patients to complete subsequent infusions successfully. When premedication is used, it should be administered approximately 30 min before initiating the infliximab infusion to allow adequate time for prophylactic medication to distribute and be clinically active. These treatment approaches are similar to those used in the management of acute infusion reactions to *i.v.* immune globulin (47, 48) and to chimeric and monoclonal antibodies used in the treatment of malignancy (49). One open study suggests that there is no advantage to routine premedication for patients with no history of an infusion reaction to infliximab (9). Rarely, severe anaphylactic or anaphylactic-like reactions may occur, with clinical signs and symptoms including hypotension, laryngeal/pharyngeal edema, severe bronchospasm, etc (33, 50–52). Health care providers should be prepared to evaluate patients experiencing severe infusion reactions for evidence of an anaphylactic or anaphylactic-like reaction, and to provide appropriate treatment with epinephrine, diphenhydramine, steroids, oxygen, nebulized β-agonists, *i.v.* fluids, and airway management as required to stabilize the patient (46, 53, 54). There is one report that 172 infliximab infusions were safely administered to 115 patients in a home-infusion setting (55). Nevertheless, given the rare occurrence of severe anaphylactic or anaphylactic-like reactions with infliximab infusions, such an approach should only be undertaken with great caution, if at all. It should be noted that in clinical trials, there has been little long-term impact of acute infusion reactions on short-term responses (39). Nevertheless, there is expanding evidence that patients who do develop HACA (the same group who are more susceptible to developing acute infusion reactions) will be more likely to lose a long-term response to repeated dosing (56). Hence, efforts are underway to identify means to reduce the development of HACA, such as repeated infusions at 0, 2, 6 wk, preconditioning with an immunosuppressive agent, or possibly administering a high dose of *i.v.* steroids before initial infusions (see below).

In the initial series of clinical trials in Crohn's disease and rheumatoid arthritis, delayed hypersensitivity-like reactions were not observed, presumably because patients were retreated within 12 wk of the initial dose. In contrast, delayed hypersensitivity-like or serum sickness-like reactions occurred in 10 of 40 Crohn's disease patients who had received initial therapy with an investigational liquid formulation of infliximab, and then subsequently undergone a 2–4 yr drug holiday before infusion with the final commercialized formulation of infliximab (a lyophilized powder that is reconstituted immediately before infusion) (57). The delayed hypersensitivity-like syndrome occurred 3–12 days after the infliximab reinfusion. Clinical symptoms included myalgia (nine of 10 patients); rash (seven of 10 patients); fever (six of 10 patients); polyarthralgias (five of 10 patients); pruritus (four of 10 patients); facial, hand, or lip edema, urticaria, sore throat, and dysphagia (each two of 10 patients); and headache (one of 10 patients). Six of the 10 patients were hospitalized and treated with antihistamines and/or corticosteroids. One patient required treatment with epinephrine. Although none of the patients had elevated HACA titers preceding the inciting dose, most patients rapidly developed high titers of HACA correlating with the onset of the serum sickness-like reaction (see below). In clinical practice, delayed hypersensitivity-like reactions have occurred, but at a significantly lower frequency than the initial reported frequency of 25% (33, 58). In one large study of patients with Crohn's disease receiving repeated doses of infliximab every 8 wk through wk 54, the frequency of delayed hypersensitivity-like reactions was approximately 2% (3). A previous episode of delayed hypersensitivity-like reaction may not be an absolute contraindication to additional infliximab therapy (59). However, patients with a history of delayed hypersensitivity-like reaction should probably receive concomitant immunosuppressive therapy and should be routinely premedicated with diphenhydramine, acetaminophen, and steroids (possibly for several days) (59). Clinicians should use good clinical judgment, and patients who have experienced particularly severe or potentially life-threatening presentations of delayed hypersensitivity-like reactions previously, such as acute respiratory distress syndrome (60), may not be ideal candidates for retreatment. Furthermore, because of the high titer of anti-infliximab antibodies that form in association with delayed hypersensitivity-like reactions (in contrast to low titers with acute infusion reactions), the benefits of infliximab are likely to be significantly reduced in these patients.

HACA

In an integrated safety data set containing 771 patients treated with infliximab in clinical trials, there were 289 patients who could be evaluated for HACA (patients with infliximab in the serum were excluded because infliximab interferes with the HACA assay) (61). Eighty of these 298 patients (28%) were HACA positive (62 patients with rheumatoid arthritis, 18 patients with Crohn's disease). The highest incidence of HACA occurred in patients who received infliximab at the lowest dose used in clinical trials (1 mg/kg). Concomitant therapy with methotrexate, azathioprine, or 6-mercaptopurine and multiple infliximab doses (three-dose induction followed by every 8 wk maintenance dosing) each seems to reduce the incidence of HACA by 2–3-fold (36, 39, 61). In the context of infliximab therapy in clinical trials, the presence of HACA has had little apparent impact on efficacy (39). However, clinical trials may not be the ideal setting to determine the effect of HACA on clinical response because many patients in the trials are receiving

ongoing infliximab dosing, and the presence of infliximab in the serum interferes with the HACA assay, making the HACA determination indeterminant in approximately half of patients (3, 39). Several recent clinical series have confirmed the observations from clinical trials that patients who develop HACA antibodies are more likely to develop acute infusion reactions, and that concurrent immunosuppressive and/or corticosteroid therapy reduces the frequency of HACA formation (56, 62, 63). In addition, these studies suggested that the presence of HACA was associated with loss of efficacy (56, 62, 63). The preliminary results from a randomized controlled trial have suggested that premedication with a single dose of *i.v.* hydrocortisone 200 mg before the infliximab infusion may reduce the frequency of HACA antibody formation by 50% to 30% (64, 65). This effect is most prominent in patients who are not receiving concomitant immunosuppressive therapy. Although the presence of HACA has been associated with an increased frequency of acute infusion reactions and possibly delayed hypersensitivity reactions, most HACA-positive patients will not experience an adverse event after retreatment with infliximab, and therefore retreatment with infliximab is not contraindicated in HACA-positive patients. Thus, at this point in time, clinicians do not need to routinely test for the presence of HACA in patients undergoing retreatment with infliximab because there is not a treatment implication if the patient is found to be HACA positive.

Autoantibody Formation and Drug-Induced Lupus

In clinical trials in patients with Crohn's disease, new ANA developed in 44% of patients initiating treatment with infliximab, and new antidouble-stranded DNA antibodies developed in 22% of patients (33). Immunosuppressive therapy was protective against developing both ANA and antidouble-stranded DNA antibodies. Six patients (three with rheumatoid arthritis and three with Crohn's disease) in a clinical trial database developed signs of drug-induced lupus (33). In a recent open label clinical experience, 7% of 116 patients with Crohn's disease initiating treatment with infliximab were positive for ANA at baseline, and the frequency of a positive ANA reaction rose to 50% after infliximab therapy, with the majority of patients becoming ANA positive after one or two infusions (66). Many of the patients who became ANA positive had increasing ANA titers over time, and some developed antidouble-stranded DNA and/or antihistone antibodies. Two of 116 patients developed clinical evidence of drug-induced lupus manifested by a butterfly rash and polyarthralgias in conjunction with a positive ANA, antidouble-stranded DNA antibody, and antihistone antibody. Again, the frequency of developing ANA seemed to be less common in patients who receive concomitant immunosuppressive therapy. Because few patients who develop a positive ANA, antidouble-stranded DNA antibody, or antihistone antibody develop clinical evidence of lupus, the presence of these antibodies in an asymptomatic patient is not a contraindication to treatment with infliximab.

Infectious Complications Including Tuberculosis

In clinical studies of infliximab, infections requiring treatment were reported in 36% of patients receiving infliximab and 26% of patients receiving placebo (33). Infections most frequently reported were respiratory tract infections (including sinusitis, pharyngitis, and brochitis) and urinary tract infections. No statistically significant increase in serious infections or sepsis was observed in infliximab-treated patients compared with placebo-treated patients. However, serious infections were observed (albeit at low frequency) in infliximab-treated patients including pneumonia, sepsis, miliary tuberculosis, and disseminated coccidioidomycoses. The administration of infliximab should be delayed in patients with known or suspected active infection, until the infection is adequately treated. In postmarketing experience, tuberculosis, histoplasmosis, listeriosis, *Pneumocystis carini* pneumonia, and aspergillosis have all been observed, and in some instances have led to patient death (33, 67–71). Of particular note, there have been over 70 reported cases of reactivation of latent tuberculosis after treatment with infliximab for a median of 12 wk (67). Forty-eight of the 70 patients developed tuberculosis after three or fewer infusions. Forty of 70 patients had extrapulmonary disease. Sixty-four of the 70 patients lived in countries with a higher endemic incidence of tuberculosis than the United States. This report has led to the recommendation that patients undergo purified protein derivative skin testing (with interpretation of the results according to their risk strata as outlined in Table 2) (75) before infliximab therapy (33). Patients who are purified protein derivative negative can proceed on to infliximab therapy. Patients who are purified protein derivative positive should undergo a chest x-ray. If the chest x-ray is normal, then patients should be treated for latent tuberculosis according to the guidelines from the American Thoracic Society (9 months of treatment with isoniazid is the preferred regimen) before initiating infliximab therapy (72). Similarly, patients with an abnormal chest x-ray will require treatment of active tuberculosis to resolution according to the guidelines from the American Thoracic Society before initiation of infliximab therapy (73). However, it must be recognized that a significant number of patients with Crohn's disease, in particular those with indications for infliximab (chronically ill patients taking steroids and/or immunomodulators), will be anergic (74). These guidelines may be considered a minimal standard, but may not prevent reactivation of tuberculosis in susceptible, but anergic, patients. Thus, when considering treatment with infliximab, the likelihood of previous exposure to tuberculosis should be considered (based on history of risk factors) and a chest x-ray ordered, in addition to skin testing, if the patient is likely to be, or proven, anergic. Similarly, patients who have received tuberculosis immunization (bacillus Calmette-Guérin) should receive a chest x-ray before infliximab therapy.

Table 2. Criteria for Measuring Tuberculin Positivity by Risk Group (75)

≥5-mm Induration	≥10-mm Induration	≥15-mm Induration
Patients with HIV	Recent immigrants from high-risk countries	Patients with no risk factors for tuberculosis
Patients with a recent contact of tuberculosis	Injection drug users	
Fibrotic changes on chest radiograph consistent with prior tuberculosis	Residents/employees of high-risk congregate settings: prisons, jails, nursing homes	
Patients with organ transplants and other immunosuppressed patients (includes immunocompromised patients, particularly those receiving corticosteroids or other immunosuppressives)	Mycobacterial laboratory personnel	
	High-risk patients including those with silicosis, diabetes mellitus, chronic renal failure, hematological disorders	
	Younger patients exposed to high-risk adults	

To evaluate patients for tuberculosis, take a thorough history, perform a physical examination, and then place a purified protein derivative (PPD) test. The PPD is injected intradermally on the forearm and examined 48–72 h later. PPD is readily available and can be administered at an outpatient office setting. If a local inflammatory reaction occurs, the patient may have been exposed to tuberculosis, but may not have active disease. Analysis of the local inflammatory reaction requires measuring the diameter of induration, and interpreting the results according to the criteria outlined in the table above. A chest x-ray should be performed if the PPD is positive or if warranted by the medical history. Anergic patients or those with prior bacillus Calmette-Guérin vaccination should have a chest x-ray performed before treatment.

CONCLUSIONS

Induction therapy with infliximab is indicated for treatment of signs and symptoms, and induction and maintenance of remission in patients with moderate to severely active inflammatory Crohn's disease with an inadequate response to conventional therapy, and for reduction in the number of draining fistulas in patients with fistulizing Crohn's disease. Emerging indications for infliximab therapy in patients with Crohn's disease include maintenance of fistula improvement (reduction in the number of draining perianal or enterocutaneous fistulas) and complete fistula response (no draining fistulas) in patients with fistulizing Crohn's disease, steroid sparing in steroid-treated patients, early use in hospitalized patients who have not failed conventional medical therapy where there is either a severe clinical presentation or a rapid onset of action is desired, and in a variety of unusual and extraintestinal manifestations of Crohn's disease. An infliximab dose of 5 mg/kg is recommended initially, but some patients who require maintenance dosing may benefit from increasing the infliximab dose over a range of 5–10 mg/kg. An induction regimen of three doses at 0, 2, and 6 wk is the preferred dosing strategy for inducing remission. The optimal dosing interval for patients who require retreatment seems to be every 8 wk for most patients. Concomitant immunosuppressive therapy with azathioprine, 6-mercaptopurine, or methotrexate may result in improved outcomes because of a synergistic effect on clinical response and/or a reduction in the frequency of HACA formation, acute infusion reactions, and a reduced risk of delayed hypersensitivity-like reactions and formation of ANA. Pretreatment with diphenhydramine (and in selected cases acetaminophen and, rarely, corticosteroids) is recommended in patients with a history of infusion reactions and patients at risk for delayed hypersensitivity-like reactions. Patients with evidence of active infection should not receive infliximab until the infection is adequately treated, and all patients should be screened for tuberculosis before initiating infliximab therapy.

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